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Review Article

Targeted Therapy for KRAS Mutant Non-Small Cell Lung Cancer

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Abstract

Approximately one third of non-small-cell lung cancer (NSCLC) cases carry activating point mutations in the KRAS oncogene. Its protein product is known as the K-Ras protein, that is a 188-amino acid protein with 21.6kDa molecular weight. The K-Ras is a major player in activating multiple cellular signaling cascades through the RAS/MAPK pathway, that can result in transformation and tumor progression.

The frequency of its mutation in NSCLC is: adenocarcinomas (20-30%) and less commonly in squamous-cell carcinoma of the lung (≈7%). Earlier research has suggested that patients with KRAS-mutant NSCLC are less likely to benefit from systemic chemotherapy and are poorer responders to EGFR-specific tyrosine kinase inhibitors. It was also defined as one of the "driver" mutation for lung and other cancers. However, KRAS so far has remained largely an undruggable target in the era of targeted and immunotherapies.

In this review, we have searched the available databases for major research study areas for potential anti-KRAS agents and their potential effectiveness. We included PubMed, and the Web of Science online databases from 2003 to 2018, also, we scanned www.ClinicalTrials.gov to search review and original articles on the available targeted therapies for KRAS mutant ($KRAS^{mut}$) NSCLC. All search results are in English. We concluded that despite of that several predictive markers were identified in NSCLC patients, few of them can be clinically used for personalized targeted therapy.

Abbreviations

EGFR - Epidermal Growth Factor Receptor
EMT - Epithelial-Mesenchymal Transition
GEMMs - Genetically Engineered Mouse Models
GSIs - γ-Secretase Inhibitor
HGF - Hepatocyte Growth Factor
HOP - HSP Organizing Protein
HSP - Heat Shock Proteins
HSEs - Heat Shock Response Elements
IGF - Insulin-Like Growth Factor
KRAS - Kirsten Rat Sarcoma Viral Oncogene Homolog
MEK - Mitogen-Activated Protein Kinase Kinase
mTOR - Mammalian Target of Rapamycin
NSCLC - Non-Small Cell Lung Cancer
OS - Overall Survival
KRAS mutant - $KRAS^{mut}$
KRAS wild type - $KRAS^{wt}$
PD-1 - Programmed Cell Death-1
PDGFR - Platelet Derived Growth Factor Receptor
PD-1 - Programmed Cell Death Ligand-1
PFS - Progression Free Survival
RR - Response Rate
SD - Stable Disease
VEGF - Vascular Endothelial Growth Factor
AHA1 - Activator of HSP90 ATPase 1

Introduction

To understand the versatile role of KRAS mutations in carcinogenesis, a scrutinizing approach must be used to cellular pathways that control growth. KRAS is located on chromosome 12 (12p12.1), spanning ≈38 kilo-bases. K-Ras, which the protein product, is a 188 amino-acids with a molecular weight of 21.6 kDa. It is one of the RAS family of G-proteins, which are a group of intracellular guanine nucleotide binding proteins with GTPase activity. They are located on l the inner face of the plasma membrane. It functions as a binary molecular switch, when it is bound to GTP, it is in an active state, and when GDP-bound, it is considered in an inactive state. While in an active state, RAS-GTP complex activates several signal

transduction cascades such as Raf-MEK-ERK, PI3K-AKT-mTOR and RalGDS-RalA/B pathways and TIAM1-RAC1 pathway. See figure 1. All play pivotal roles in cellular proliferation, apoptosis, survival and growth. Putting a RAS proteins in an active RAS-GTP conformation is achieved through multiple triggering signals from growth factors, like EGFR that favor a constitutive activation of KRAS, and also HGF and IGF when they interact with their receptors. The hydrolysis rate constant (kh) is of K-Ras is too low to be physiologically relevant, but specific "GTPase activating proteins" can increase hydrolysis by 100,000-fold. These are Guanine nucleotide exchange factors (GEFs), which decrease the affinity of RAS proteins for GDP and favor GTP binding resulting in RAS activation, while GTPase-activating proteins (GAPs) accelerate the intrinsic GTPase activity to regulate the RAS cycle [1]. KRAS mutations are thus one of the driver mutations, and the gene is one of the principle oncogenes such as Raf, Myc, Src, Abl/Bcr and c-erbB-2. KRAS^{mut} were first described more than 40 years ago. They are usually missense mutations with an amino acid substitution at codons 12,13 or 61. Eighty percent of these mutations are in codon 12. The most common mutation is G–T transversion in 70% of tumors.

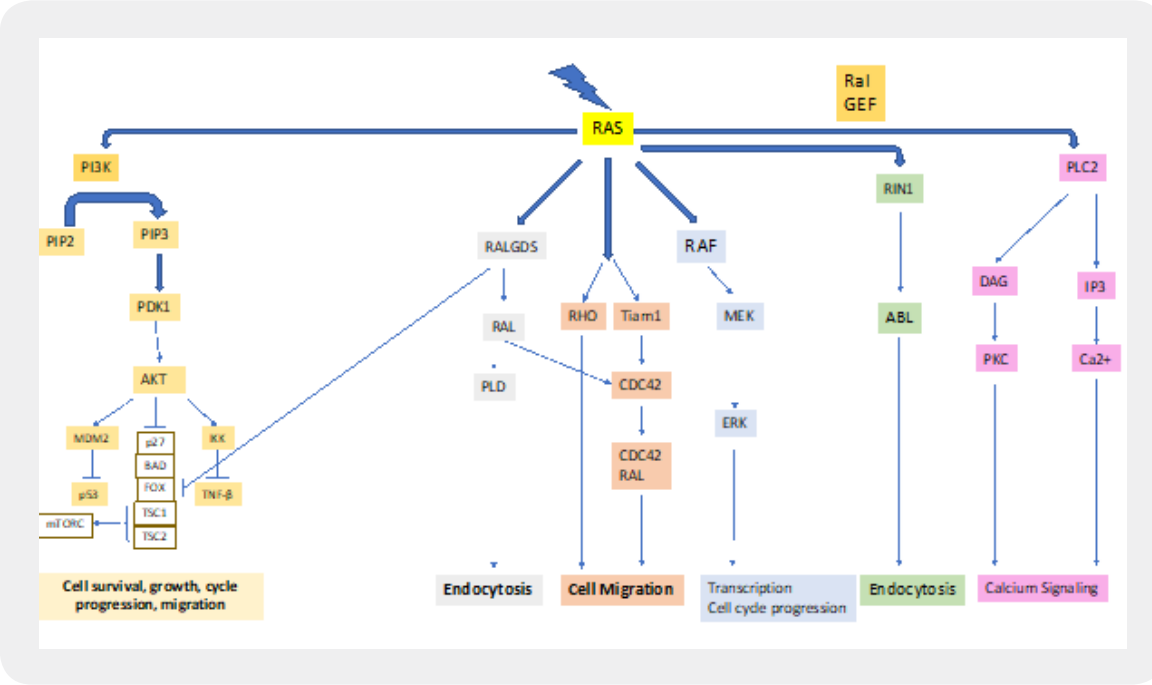

Figure 1: *The figure illustrates some of the downstream signaling pathways in KRAS^{mut} NSCLC.*

In 2005, Mascaux at al reported a meta-analysis to evaluate the prognostic value of KRAS^{mut} in lung cancer. Their study included 43 studies published from 1990 till 2003 with a total number of 5216 patients included in the meta-analysis. The authors concluded that RAS is a prognostic factor for lung cancer and KRAS was associated with poorer outcomes in NSCLC patients [2]. Another meta-analysis by Meng *et al* was published in 2013 reported similar results as they reported that KRAS^{mut} was associated with worse OS in NSCLC patients with HR of 1.45 (95% CI: 1.29-1.62). They also found that this is observed more the adenocarcinoma patients and interestingly enough in earlier stages [2].

Approximately one third of NSCLC cases carry activating point mutations in KRAS oncogene, mainly adenocarcinomas, and research has suggested that patients with $KRAS^{mut}$ NSCLC fail to benefit from systemic chemotherapy compared to their $KRAS^{wt}$ peers. Moreover, subgroup analysis has revealed that of these patients lack sensitizing EGFR mutations meaning the two mutations are mutually exclusive as well, thus targeted EGFR therapies cannot benefit these patients as well. Despite their high frequency in clinical settings and the vast amount of research done this field, $KRAS^{mut}$ NSCLC still lack active treatment agents that target its specific oncogenic effects.

In this review, we searched Pubmed and Web of Science data bases from 2003 -2018 as well as www.ClinicalTrials.gov to find published and ongoing therapeutic trials specifically targeting $KRAS^{mut}$ NSCLC.

Serine/Threonine Kinase Inhibitors

Phenformin, an analogue of the anti-diabetic drug metformin, and is an inhibitor of mitochondrial-induced apoptosis in cells defective in LKB1. LKB1, also called STK11, is the major upstream kinase that activates AMPK. About 30% of pulmonary adenocarcinomas have mutations that inactivates LKB1 so that the cells are less capable of sensing the metabolic effort.

In a preclinical study conducted in $KRAS^{mut}$-dependent mouse models of NSCLC, the antitumor effect of the drug *phenformin* was evaluated and the results showed selective responses to phenformin in tumors with both KRAS and Lkb1 mutations as a single agent. This was translated as prolonged survival in murine models [3].

In 2014, the same concept was investigated by a group of researchers using a panel of patient derived xenografts [4]. They used both metformin and phenformin to treat the xenografts and the tumors showed significant reduction in tumor volumes after 3 weeks of treatment. The tumors also maintained the response after caseation of the treatment. Lately, reports have emerged showing that Lkb1 mutations can be a cause for PD-1 resistance in $KRAS^{mut}$ NSCLC adenocarcinoma [5]. Reportedly, combined KRAS and Lkb1 mutation had 7.4% RR to PD-1 inhibitors compared to 28.6% RR in $KRAS^{mut}$ only cases. Also, lkb1 mutations were found to be associated with lack of PD-L1 expression on tumor cells.

mTOR is one of the major druggable targets in cancer since it falls at the interface of two major pathways PI3K and LKB1. Both pathways are a is activated in $KRAS^{mut}$ tumors [6,7], and through which KRAS controls cellular growth and proliferation. Ridaforolimus is a small-molecule mTOR inhibitor and a serine/threonine kinase inhibitor. Its effectiveness as a therapeutic agent in advanced $KRAS^{mut}$ NSCLC stage IIIB/IV who failed prior treatment, was studied in a randomized trial that included 79 patients [8]. The study reported overall RR of 1% at 8 weeks of initial treatment with ridaforolimus, however, the responders who received ridaforolimus after 8 weeks showed higher median PFS compared to placebo (4 months versus 2 months; HR 0.36, p=0.09). Overall survival from randomization was 18 months in the ridaforolimus arm and 5 months in the placebo group (HR 0.46, p = 0.09).

Heat Shock Protein (HSP) Inhibitors

HSPs are a family of proteins produced by cells in response to stresses. They act as chaperones stabilizing new proteins and ensuring their proper folding or by helping to refold damaged proteins [9,10]. HSP transcription occurs in response to heat shock factors (HSFs) that recognize the DNA enhancer sequences and heat shock response elements (HSEs) [11]. They recruit proteins through a complex of HSP70 and HSP40 co-chaperones, linked by an adapter molecule HOP (HSP organizing protein). The complex binds to a dimer of HSP90 protein bound to ADP. ADP-ATP exchange happens, that is activated by an adapter protein AHA1 (Activator of HSP90 ATPase 1), and allows a conformational change thus protecting the protein recruited, so that it can perform its functions. In this exchange of ATP, the recruited protein is coupled to ubiquitin and then shuttled to a proteasome [12]. Many proteins involved in cell proliferation and survival are clients of HSPs including receptor tyrosine kinases (RTKs), such as EGFR, ERBB2, KIT, MET, intracellular kinases, such as B-RAF, AKT and CDK4 factors transcript as p53, HIF1α or estrogen receptor, or protein as APAF1, BCL2 and telomerase. The HSP enable these proteins to withstand the hypoxic and acidic environment inside the tumor. They will even allow them to tolerate oncogenic genetic variations that would otherwise be lethal. HSPs are overexpressed in many solid tumors and hematological malignancies and they contribute to oncogenesis, having a positive effect on tumor cell survival and proliferation [13,14].

The activity of *ganetespib* (Synta Pharmaceuticals), a small molecule inhibitor of Hsp90 was examined in a panel of NSCLC cell lines harboring a wide range of KRAS mutations. *In vitro*, ganetespib demonstrated cytotoxicity through destabilization of the signaling effectors of activated K-RAS. Low concentrations of ganetespib in combination with MEK or PI3K/mTOR inhibitors resulted in enhanced cytotoxic compared to single agents in a subset of $KRAS^{mut}$ cells. Consistent with this finding, the antitumor activity of ganetespib was increased by combining it with the irreversible PI3K/mTOR inhibitor, BEZ235 in human A549 xenografts in nude mice. At the molecular level, ganetespib abolished the activation of signaling feedback loops that are produced in response to inhibition of MEK and PI3K/mTOR, although this activity was not the sole determinant of the combinatorial advantage. Ganetespib in NSCLC cells harboring $KRAS^{mut}$ enhanced the antimitotic effect of chemotherapy such as topoisomerase inhibitors and alkylating agents. These data highlight the promise of ganetespib as a single-agent or in combination of $KRAS^{mut}$-driven lung tumors [15].

A phase II trial, studied another HSP inhibitor, NVP-AUY922 (Institute for Cancer Research/Vernalis), and attempted to identify predictors of response [16]. The *in vitro* effects of NVP-AUY922 on proliferation and protein expression in NSCLC cell lines showed changes in gene expression induced by exposure to the investigated agent. These results were evaluated in xenograft models for tumor control and biological effects. NVP-AUY922 was found to be a potent inhibitor of *in vitro* growth in 41 NSCLC cell lines evaluated with an IC_{50} <100 nM, IC_{100} and in 36 of the 41 cell lines tested at <40 nM. This was in accordance with changes in the gene expression after exposure to NVP-AUY922 that is involved in wide range of cellular functions, including steadily decreasing dihydrofolate reductase (DHFR) expression. NVP-AUY922 slowed the growth of A549 ($KRAS^{mut}$) xenografts and decreased EGFR protein expression in H1975 xenografts harboring a sensitizing EGFR mutation. A phase Ib trial was published in October 2018. They recruited 9 patients with previously-treated metastatic non-squamous NSCLC were treated using a standard 3 + 3 design with pemetrexed at the standard 500mg/m^2 dose, plus: AUY922, however the study was closed due

inability to obtain the investigational agent but the researchers reported a maximum tolerated dose of AUY922 with pemetrexed of 55mg/m^2. No reports about KRAS^{mut} were published [17].

MEK Inhibitors

Since KRAS mutations result in the activation of the RAF-MEK-ERK pathway, MEK inhibitors are thought as potential therapeutic agents for KRAS^{mut} NSCLC. MEK inhibitors are thought to confer their anti-cancer effects by stabilizing the pro-apoptotic BH3-only protein, BIM and BAD, and destabilization of MCL1 which a member of Bcl-2 family [18]. However, their effects in clinical setting were limited [19]. Recent approach of double hit combination therapy to increase the sensitivity to a certain agent [20,21] has led researchers to investigate the possibility of adding a Bcl-2 family inhibitor can increase the efficacy of a MEK inhibitors in this subset of patients. A group of researchers treated a panel of 53 NSCLC and pancreatic cancer cell lines with a combination of *navitoclax* (ABT-263, Abbott Laboratories), a Bcl-2/Bcl-xL (BCL2/BCL2L1) antagonist, and a novel MEK inhibitor, G-963. The combination yielded a synergistic effect in the majority of lines, with more cell lines harboring KRAS mutations in the highly synergistic group. Cells exposed to G-963 were found to be arrested in G1 phase with only a small fraction actually undergoing apoptosis. The addition of *navitoclax* to G-963 greatly increased the percentage of cells that underwent apoptosis with no change observed in the cell cycle arrest part. Same combination was more effective than either single-agent in the KRAS^{mut} H2122 xenograft model; BIM stabilization was observed in the tumors which is consistent with the mechanism of action observed in cell culture. Addition of the phosphatidylinositol 3-kinase (PI3K, PIK3CA) inhibitor, GDC-0941, to this treatment combination increased cell killing compared to double or single-agent treatment. Taken together, these data suggest the efficacy of agents that target the MAPK and PI3K pathways that can be improved by combination with a Bcl-2 family inhibitor [22]. Accordingly, other MEK inhibitors are currently under investigation, including Salirasib [23], Tivantinib [24] (MET inhibitor), trametinib (which showed a good activity in metastatic melanoma with GNQ mutations) [20] and others [25-27]. All reported initial response to the investigational agents, however, they all await multicenter trails to be used in clinical practice.

Secretory Phospholipase A_2

The approach to investigate early on biomarkers that have screening, early diagnostic, predictive and prognostic value became the mainstay for cancer research. The aim is to find cost effective, less time consuming, specific markers to determine a predict tumor behavior and plan the treatment accordingly [20,28]. One of these molecules is the isoenzyme group IIa secretory phospholipase A_2(sPLA$_2$IIa). In one study, sPLA$_2$IIa was found to have significantly elevated levels in lung cancer patients [29], and hence this enzyme is involved in tumor promoting eicosanoids it was rendered as a potential biomarker. Another group investigated its correlation with KRAS^{mut} tumors in lung [30]. They found that sPLA$_2$IIa expression correlates with increasing stage of KRAS^{mut} lung tumors. Since the same group reported sPLA$_2$IIa inhibitors cytotoxic effect correlate with sPLA$_2$IIa expression, it was hypothesized that sPLA$_2$IIa modulates lung cancer cell growth in KRAS^{mut} cells. This opens the field for a new druggable target in this subset of patients, especially advanced cases.

Antiangiogenic Agents

Sorafenib, a small molecule inhibitor of several receptor tyrosine kinases such as VEGFR2, PDGFR, KIT as well as pathways such as Raf, was also investigated in several studies [31-34]. In a phase II trial, 59 patients with $KRAS^{mut}$ lung cancer who previously received platinum-based therapy and stage IIb or IV were treated with sorafenib. The median PFS was 2.3 months median overall survival (OS) was 5.3 months. Patients with a prediction of good prognosis according to VeriStrat serum proteomics assay showed a significantly superior PFS [HR, 1.4; 95% confidence interval (CI), 1.0-1.9] but not OS (HR, 1.3; 95% CI, 0.9-1.7). Another, phase II trial, the Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE-1), the disease control rate for patients treated with sorafenib was 61% in patients with KRAS mutations versus 56% in those with wild type KRAS. And a third phase II study of sorafenib carried out in 37 previously treated patients with non-small cell lung cancer were 11 patients (32%) had KRAS mutations. The disease control rate observed in these patients was not significantly different at 60% versus 71% in those with KRAS wild-type tumors (p=0.69).

Hedgehog Pathway Inhibitors

The hedgehog pathway is a group of intracellular signaling family of proteins. They were first isolated in the early 1990s and they are known to play a fundamental role in embryonic development including regulation of cellular proliferation, differentiation, epithelial to mesenchymal transition (EMT) and stem cell renewal and differentiation [35,36]. In adults, loss of some components of hedgehog functions was found in some hereditary diseases, however, in cancer overexpression of these proteins was reported, such as basal cell carcinoma, colon, lung, and pancreas cancer [37-39]. Also, hedgehog signaling has been implicated in tumor recurrence by promoting the survival of tumorigenic precursors and their effects on the tumor-associated stroma during advanced NSCLC [40,41]. One report evaluated the effects of the combination of an inhibitor targeting the hedgehog pathway combined with radiation in NSCLC cell lines *in vitro* using an A549 xenograft model [42]. They looked at tumor growth, proliferation, apoptosis, and gene expression changes after radiotherapy and concomitant HhAntag, a hedgehog signaling antagonist. In a transgenic mouse model of $KRAS^{mut}$ (G12D)-induced lung adenocarcinoma and induced TWIST1, they evaluated the tumor response using micro-computerized tomography (CT). They found that in 4 human lung cancer cell lines, HhAntag showed little or no effect on radiosensitivity. By contrast, in both the human tumor xenograft and murine inducible transgenic models, HhAntag enhanced radiation efficacy and delayed tumor growth. This was associated with down-regulation of the hedgehog pathway in stromal cells resulting in cellular apoptosis.

A USA group of investigators published preliminary data in 2018 based on analysis of human lung cancer xenografts and preclinical Genetically Engineered Mouse Models (GEMMs) of $KRAS^{mut}$ NSCLC. They found that "the epithelial-mesenchymal transition (EMT) status of tumor cells is critical to their therapeutic response to MEK inhibitors", with the epithelial state show high sensitivity to MEK inhibitors and the mesenchymal state results resistance to therapy [43]. This point can be an entry point to hedgehog inhibitor role in $KRAS^{mut}$ NSCLC.

Notch Pathway Inhibitors

Notch pathway is an evolutionary conserved signaling pathway. It mediates short-range signaling cell to cell intercommunications [44]. Notch receptor ligands are transmembrane proteins [45] that result in NOTCH cleavage by γ-secretase complex [44]. One of the KRAS oncogenic mediators is Discoidin Domain Receptor 1 (Ddr1) gene which encodes a receptor protein kinase [46]. Ddr1 activates cell proliferation through a NOTCH dependent pathway [47]. So, the role of this pathway in the generation and maintenance of $KRAS^{mut}$ (G12V)-driven NSCLCs was studied using γ-secretase inhibitor (GSIs) [48]. The investigators were able to show that γ-secretase is essential for NSCLC development, and pharmacological treatment of mice carrying autochthonous NSCLCs with a GSI inhibited cancer growth. In another research, the investigators utilized dual treatment of TP53-mutant patient-derived lung xenografts (PDX) with Ddr1 and NOTCH inhibitors, $KRAS^{mut}$ showed regression with efficacy comparable to standard chemotherapy [49].

SRC-TKI Inhibitors

Both Src protein levels and Src protein kinase activity, are frequently elevated in human cancers in comparison to adjacent normal tissues. Moreover, these levels appear to increase with the stage of disease [50]. And in 2016, a study by Zhou *et al* has reported that $KRAS^{mut}$ NSCLC patients had SRC expression levels that is as comparable to non-mutant cases [51]. Pemetrexed is an antifolate agent that is widely used to treat NSCLC. Resistance to pemetrexed is associated with thymidylate synthase (TYMS) overexpression. Using a Src inhibitor was reported to improve response to pemetrexed in these cases and even revert the developed resistance. The researchers noticed a positive correlation between TYMS and Src transcript levels. So, a combination of Src inhibitors with pemetrexed were attempted *in vitro* as means to improve the patients' response to pemetrexed [21,52]. However, this hypothesis requires a thorough investigation of TYMS and Src overexpression, protein level and activity and KRAS mutations in NSCLC.

Farnesyltransferase Inhibitors and Trans-Farnesylthiosalicylic Acid

As mentioned before, RAS proteins are membrane-bound intracellular GTPases. In fact, to exert their full signaling effects they need to remain in this membrane-bound status. The enzyme farnesyl protein transferase initiates binding of RAS protein to the membrane and hence using farnesyl protein transferase inhibitors in the human colon carcinoma cell line DLD-1. However, H-Ras only showed response to treatment, meanwhile K-Ras and N-Ras remained in a membrane -bound state [53]. Salirasib is an s-trans, *trans*-farnesylthiosalicylic acid which was found to prevent membrane binding in all forms of Ras proteins in contrast to farnesyl protein transferase inhibitors [53,54]. Salirasib was investigated in a phase I trial and showed good tolerance to treatment [55]. Recently, results from another phase I study in japanese patients was published. The agent was used as oral twice daily dose in 21 solid tumor patients who failed previous treatments. Only 4 cases tested $KRAS^{mut}$ positive, however, they achieved a remarkable median PFS of 227 days [56].

Immunotherapy and Other Promising Approaches

Programmed death 1 (PD-1) is a key immune-checkpoint receptor expressed by activated T-cells and mediates immunosuppression within the tumor microenvironment. Overexpression of the PD-1 ligand (PD-L1) has been reported in NSCLC [57]. Since anti-PD-1 and PD-L1 been used in NSCLC therapy, the estimated 5-year OS rate was 16% for patients with pretreated, advanced NSCLC [58]. Thorough research showed that many NSCLC cell-lines with KRAS, EGFR and BRAF mutations, and ALK or RET rearrangements have high levels of PD-L1 expression, randomized phase III trials results indicated that patients with *EGFR* mutations exhibit less efficacy of anti-PD-1/PD-L1 treatment than those with wild-type *EGFR*. Meanwhile, $KRAS^{mut}$ were found to be more likely to be predictors of favorable outcomes [59,60]. These results were particularly true for nivolumab, but not for atezolizumab [61,62]. Even though these results are very promising, the molecular bases are not well understood, yet. A group of researchers tried knocking down KRAS or ERK2 using siRNAs or ERK2 inhibitors, and this resulted in decreased PD-L1 expression in $KRAS^{mut}$ NSCLC with PD-L1 overexpression. Same effect was observed with MEK inhibitors [63-65].

K-Ras(G12C) Inhibitors

In 2013, Ostrem *et al* published a report about small molecules that can irreversibly bind to K-Ras(G12C) mutant form only [66]. K-Ras(G12C) is a form of mutant K-Ras protein in which a transversion at 34^{th} nucleotide occurs and glycine at residue 12 is replaced with cysteine (G12C) [67]. The K-Ras(G12C) inhibitors bind to the mutant cysteine thus sparing wild forms. After binding, they result in disruption in the K-Ras protein crystal structure so that its affinity to GDP becomes higher than GTP [66]. Later other reports emerged about different forms of K-Ras(G12C) inhibitors such as SML-8-73-1 which binds in a manner similar to GDP [68], and SML-10-70-1 which is a partially caged version of SML-8-73-1, which allows better transportation across cell membranes [69]. The results from these agents are very promising with high specificity to tumor tissue since the drug has minimal affinity to wild type K-Ras and good potency.

Discussion

Lung cancer is known for its high incidence, prevalence and lethality, both due to disease or other condition based complications [70,71]. However, it is known for its diverse subtypes that pose a challenge to current clinical practices and resistance to therapies [28,72-74]. NSCLC represent the majority of this group (80%) with KRAS mutations identified in in 20-30% of adenocarcinomas and less so in squamous-cell carcinomas of the lung [70]. This subset of patients was identified as worse responders to current therapies [75], and despite the fact that KRAS is a driver mutation in NSCLC with relatively well described downstream signaling effects, no definite therapy has been developed targeting its effects. Due to its diverse effects on the signaling pathways, $KRAS^{mut}$ NSCLC are most likely to be targeted by combination therapies. However, due to the complexity of the downstream signals affect by mutant K-Ras active form, the aforementioned arsenal of therapies needs to be addressed in trials to assess efficacy, responses and safety. Meanwhile, approved agents can be preferentially used by oncologists in clinics according to current guidelines, but with attention to agents who shows anti-KRAS activity in preclinical studies. This approach will put PD-1/PD-L1

inhibitors early in the list, so as sorafenib, ridaforolimus, busotinib and salirasib among others mentioned in our review.

Stepping into a targeted combination therapy is plausible to be the focus of the preclinical studies. Lung cancer treatment have not seen much improvements in the standard of care treatments for the past 50 years, till the introduction of PD-1/PD-L1 inhibitors. This requires a better understanding of downstream signaling pathways that are affected by KRAS. So, more focus should be invested in this area.

Table 1: *KRAS common sites of point mutations in non-squamous NSCLC* [76].

KRAS gene mutation
12p12.1
13
61

Table 2: *Lists ongoing clinical trials of novel agents in KRAS mutant NSCLC* [40].

	ClinicalTrials.gov identifier	Study	Aim of the study	Estimated enrollment
1	NCT03170206	Phase I/II Study of the CDK4/6 Inhibitor Palbociclib (PD-0332991) in Combination With the MEK Inhibitor Binimetinib (MEK162) for Patients With Advanced KRAS Mutant Non-Small Cell Lung Cancer	Study of the CDK4/6 Inhibitor Palbociclib (PD-0332991) in Combination With the MEK Inhibitor Binimetinib (MEK162) for Patients With Advanced KRAS Mutant Non-Small Cell Lung Cancer	72
2	NCT01859026	A Phase I/IB Trial of MEK162 in Combination With Erlotinib in Non-Small Cell Lung Cancer (NSCLC) Harboring KRAS or EGFR Mutation	The main purpose of this study is to find out if the drugs MEK162 and erlotinib (Tarceva) given in combination are safe and have beneficial effects in patients who have NSCLC. The U.S. Food and Drug Administration (FDA) has not approved MEK162 for use to treat NSCLC. Erlotinib is an FDA approved drug for the treatment of Non-Small Cell Lung Cancer.	44

3	NCT03299088	Pembrolizumab and Trametinib in Treating Patients with Stage IV Non-Small Cell Lung Cancer and KRAS Gene Mutations	This phase Ib trial studies the side effects of pembrolizumab and trametinib in treating patients with non-small cell lung cancer and KRAS gene mutations that has spread to other places in the body. Monoclonal antibodies, such as pembrolizumab, may interfere with the ability of tumor cells to grow and spread. Trametinib may stop the growth of tumor cells by blocking some of the enzymes needed for cell growth. Giving pembrolizumab and trametinib may work better in treating patients with non-small cell lung cancer.	42
4	NCT02022982	Phase I/II Study of the CDK4/6 Inhibitor Palbociclib (PD-0332991) in Combination with the MEK Inhibitor PD-0325901 for Patients with KRAS Mutant Non-Small Cell Lung Cancer and Other Solid Tumors	This research study is evaluating the experimental drug palbociclib in combination with another experimental drug PD-0325901 as a possible treatment for cancers with KRAS mutations, particularly for those which started in the lung	139
5	NCT03520842	Study of Regorafenib in Combination with Oral Methotrexate for KRAS Mutated Non-Small Cell Lung Cancer (NSCLC) Actual Study Start Date: August 14, 2018 Estimated Primary Completion Date: September 1, 2019 Estimated Study Completion Date: June 1, 2020	This phase II trial studies how well regorafenib works together with methotrexate in treating participants with metastatic non-squamous non-small cell lung cancer with tumors that harbor a **KRAS** mutation. Regorafenib is a targeted therapy that works on different cancer pathways to stop the growth of tumor cells and stop them from spreading. Methotrexate may stop the growth of tumor cells by blocking some of the enzymes needed for cell growth. Giving regorafenib and methotrexate together may work in treating participants with **KRAS** mutated non-small cell lung cancer.	18

6	NCT03704688	Phase 1 Trial of Trametinib and Ponatinib in Patients with KRAS Mutant Advanced Non-Small Cell Lung Cancer	The purpose of this study is to evaluate the safety of the combination of ponatinib and trametinib as well as the most appropriate dosages of the combination.	37
7	NCT01833143	Phase 2 Trial of Bortezomib in KRAS-Mutant Non-Small Cell Lung Cancer in Never Smokers or Those with KRAS G12D	The purpose of this study is to test the drug Bortezomib to see how well it works. The investigators want to find out what effects, good or bad, it has on patients with a limited smoking history or who have a specific mutation associated with their lung cancer.	25
8	NCT02642042	Phase II Trial of Trametinib With Docetaxel in Patients with KRAS Mutation Positive Non-Small Cell Lung Cancer (NSCLC) and Progressive Disease Following One or Two Prior Systemic Therapies	This phase II trial studies how well trametinib and docetaxel work in treating patients with stage IV KRAS mutation positive non-small cell lung cancer or cancer that has come back. Trametinib may stop the growth of tumor cells by blocking some of the enzymes needed for cell growth. Drugs used in chemotherapy, such as docetaxel, work in different ways to stop the growth of tumor cells, either by killing the cells, by stopping them from dividing, or by stopping them from spreading. Giving trametinib with docetaxel may work better in treating non-small cell lung cancer.	53
9	NCT03681483	Phase 1 Trial of RO5126766 (CH5126766) in Patients With Advanced KRAS-Mutant Lung Adenocarcinomas	The purpose of this study is to test the safety of RO5126766 at different doses to find out what effects, if any, it has on people with advanced lung cancer who have previously received treatment with a PD-1 or PD-L1 inhibitor.	31

10	NCT01912625	Phase 1 Study of Trametinib in Combination with Chemoradiation for KRAS Mutant Non-small Cell Lung Cancer	This phase I trial studies the side effects and the best dose of trametinib when given together with combination chemotherapy and radiation therapy in treating patients with stage III non-small cell lung cancer that cannot be removed by surgery. Trametinib may stop the growth of tumor cells by blocking some of the enzymes needed for cell growth. Drugs used in chemotherapy, such as carboplatin and paclitaxel, work in different ways to stop the growth of tumor cells, either by killing the cells, by stopping them from dividing, or by stopping them from spreading. Radiation therapy uses high energy x-rays to kill tumor cells. Giving trametinib, combination chemotherapy, and radiation therapy may be a better treatment for non-small cell lung cancer.	16
11	NCT01933932	Phase III, Double-Blind, Randomized, Placebo-Controlled Study to Assess the Efficacy and Safety of Selumetinib (AZD6244; ARRY-142886) (Hyd-Sulfate) in Combination With Docetaxel, in Patients Receiving Second Line Treatment for KRAS Mutation-Positive Locally Advanced or Metastatic Non-Small Cell Lung Cancer (Stage IIIB - IV) (SELECT 1)	The purpose of this study is to assess the efficacy of selumetinib in combination with docetaxel (75mg/m2) vs placebo in combination with docetaxel (75mg/m2) in patients with locally advance or metastatic NSCLCs that harbor mutations of KRAS. This study will also assess the PK, safety, patient reported outcomes (PRO) and tolerability profile of the selumetinib/docetaxel combination, compared to placebo in combination with docetaxel	510

12	NCT02152631	JUNIPER: A Randomized Phase 3 Study of Abemaciclib Plus Best Supportive Care Versus Erlotinib Plus Best Supportive Care in Patients With Stage IV NSCLC With a Detectable KRAS Mutation Who Have Progressed After Platinum-Based Chemotherapy	The main purpose of this study is to evaluate how safe and effective the study drug known as abemaciclib is in participants with lung cancer.	453

Conflicts of Interests

The article is free from any conflict of interests.

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